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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,493	02/27/2004	Susanne Leonhartsberger	LEONHARTSBERGER ET AL 1	8053

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,493	LEONHARTSBERGER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/04,6/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-18 are pending.

Specification

1. The use of trademarks has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. See, for example, "Develosil" on page 24, line 5. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Priority

2. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to GERMANY 103 09 856.9 filed on 03/06/2003. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 6/14/2004 and 6/24/2004 are acknowledged. It is noted that while the Examiner has considered the handwritten information disclosure statements, some of the entries cited in the IDS may be difficult to read as they are not all legibly written. Since all papers which are to become a part of the permanent records of the USPTO must be legibly written, and to avoid any delays in publication if the instant application were to be issued as a patent, Applicant is requested to provide a typewritten substitute copy of these information disclosure statements.

Drawings

4. The drawings submitted on 2/27/2004 have been reviewed and is accepted by the examiner.

Claim Objections

5. Claim 1 is objected to due to the recitation of "said bacterial strain secreting SAM into said culture medium and said SAM being removed...". For clarity and consistency with commonly used claim language, it is suggested the term be amended to recite "secretion of SAM by said bacterial strain into said culture medium, and removing SAM from said culture medium", or similar. Appropriate correction is required.

6. Claims 4-7 are objected to due to the recitation of "(SEQ ID NO: 1)". This appears to be a typographical error. It should be amended such that the parentheses are removed. Appropriate correction is required.

7. Claims 11-14 and 18 are objected to due to the recitation of "claims 1". This appears to be a typographical error. It should be amended to read "claim 1". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 (claims 2-18 dependent thereof) is indefinite in the recitation of "culturing a bacterial strain obtainable from a starting strain and having increased SAM synthetase activity compared to said starting strain" for the following reasons. There is no definition of the term "obtainable" in the specification. In its broadest reasonable interpretation, the term "obtainable" is equivalent to "can be

obtained". Thus, the bacterial strain may or may not be obtained from a starting strain. If it is not obtained from a starting strain, then the term "compared to a starting strain" would be indefinite as no starting strain would be involved. For examination purposes, it will be assumed that the term "obtainable" reads "obtained". Correction is required.

11. Claims 4-7 are indefinite in the recitation of "wherein the SAM synthetase used" as there is no antecedent basis for the term "SAM synthetase" in claim 1, from which claims 4-7 depend. It is noted that the antecedent basis in claim 1 is for "SAM synthetase activity". For examination purposes, it will be assumed that the claims recite "wherein the SAM synthetase activity increased is that of a protein comprising....". Correction is required.

12. Claim 11 is indefinite in the recitation of "culturing conditions over a period of 16-150 h and in the range of the growth temperature optimal for the particular bacterial strain" as it is unclear and confusing. As written one cannot determine if the temperature for culturing is the temperature at which growth is optimal for a particular bacterial strain, or if culturing is carried out at a temperature range which encompasses the temperatures at which growth is observed for a particular bacterial strain. For examination purposes, it will be assumed that the term reads "culturing conditions over a period of 16-150 hours at an optimal growth temperature for a particular bacterial strain". Correction is required.

13. Claims 12-17 are indefinite in the recitation of "L-methionine/D,L-methionine is added to the minimal salt medium" as there is no antecedent basis for the term "minimal salt medium" in claim 1, from which these claims depend. For examination purposes, it will be assumed that claims 12 and 15 depend from claim 8, claims 13-14 depend from claim 12, and claims 16-17 depend from claim 15. Correction is required.

14. Claim 18 is indefinite in the recitation of "selected from the group consisting of subsequent chromatographic purification" for the following reasons. While one of skill in the art would know what "chromatographic purification" is, the term "subsequent chromatographic purification" is unclear

because one of skill in the art cannot determine if this is a new type of purification method. If the term "subsequent" is meant to refer to an additional purification step after centrifugation, the claim should be amended accordingly. For examination purposes, it will be assumed that SAM is recovered by centrifugation of the culture medium and a subsequent purification step selected from the group consisting of chromatographic purification, complexing, filtration, cross flow filtration, and precipitation. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 8-18 are directed to a method for the production of S-adenosylmethionine (SAM), wherein said method comprises culturing a bacterial strain, including *Escherichia* strains, modified such that the enzymatic activity of a genus of SAM synthetases having any structure is increased by any means, and wherein said bacterial strain secretes SAM into the culture medium. Claims 4-7 are directed to the method of claim 1, wherein the genus of SAM synthetases is limited to SAM synthetases having greater than 40%, 60%, or 80% sequence similarity to the polypeptide of SEQ ID NO: 1.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]

chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of SAM synthetases and unknown secretion mechanisms for SAM in bacterial cells. It is noted that the specification teaches that there is no SAM transport system in *E. coli* or other bacterial strains (page 4, last paragraph). Post-filing art by Tucker et al. (J. Bacteriol. 185(10):3031-3035, May 2003) discloses the first bacterial (*R. prowazekii*) AdoMet (SAM) transporter (page 3031, right column, first complete paragraph). In addition, the claims require unknown methods to increase the enzymatic activity of a protein, such as (1) mutations in the coding region of a gene encoding the protein which would increase its enzymatic activity, (2) the presence of enhancers of that enzymatic activity which can be chemicals or the products of other genes, (3) mutations in the regulatory region of a gene encoding said protein, and (4) the presence of transcription enhancers which can be chemicals or the products of other genes.

While the specification and/or the art disclose SAM synthetases from a limited number of organisms, including *E. coli*, and increase in the enzymatic activity of the *E. coli.* SAM synthetase by transforming a bacterial cell with an inducible plasmid containing the gene encoding the *E. coli* SAM synthetase (metK), the specification fails to disclose the structure of all the genes from all organisms

which encode SAM synthetases, the structural elements required in any structural homolog of the *E. coli.* SAM synthetase (SEQ ID NO: 1) which are essential for SAM synthetase activity, which structural elements in the polypeptide of SEQ ID NO: 1 can be modified to obtain a structural homolog as recited displaying the same SAM synthetase activity as that of the polypeptide of SEQ ID NO: 1, how to secrete SAM from any bacterial cell, or other methods to enhance enzymatic activity beyond using a strong promoter or increasing the copy number of the gene of interest.

The claims require a genus of proteins which are either structurally unrelated or highly variable in structure. A sufficient written description of a genus of proteins may be achieved by a recitation of a representative number of proteins defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, either there is no structural feature recited which is representative of all the members of the genus of proteins required, or the structural feature recited, e.g., "40% sequence similarity", does not constitute a substantial portion of the genus as the remainder of the structure of any protein having the recited activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. In addition, there is no information as to a correlation between the structures disclosed/known in the art and the required enzymatic activity. Furthermore, while one could argue that the structures of known SAM synthetases are representative of all members of the genus of SAM synthetases required, such that the claimed invention is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation,

therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the enzymatic activity required has been provided, one cannot reasonably conclude that the known structures are representative of all the SAM synthetases required in the claimed invention.

Due to the fact that the specification only discloses (1) the *E. coli* and rat SAM synthetases of SEQ ID NO: 1 and 11, (2) the production of SAM in *E. coli*, and (3) a single method to increase enzymatic activity, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

17. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of S-adenosylmethionine (SAM) comprising the steps of (1) culturing an *E. coli* cell modified such that the enzymatic activity of the *E. coli* SAM synthetase of SEQ ID NO: 1 is increased by transforming said *E. coli* cell with a plasmid that comprises a nucleic acid encoding the polypeptide of SEQ ID NO: 1 linked to an inducible promoter, and (2) recovering said SAM, does not reasonably provide enablement for a method for the production of SAM comprising the steps of (1) culturing any bacterial strain, or any *Escherichia* strain, modified by any means such that the enzymatic activity of any SAM synthetase, or any SAM synthetase having greater than 40%, 60% or 80% structural similarity to the polypeptide of SEQ ID NO: 1, is increased, and (2) secreting SAM to the culture medium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence

and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 1-18 are so broad as to encompass (1) a method for the production of S-adenosylmethionine (SAM), wherein said method comprises culturing a bacterial strain, including *Escherichia* strains, modified such that the enzymatic activity of any SAM synthetase having (1) any structure, or (2) at least 40%, 60% or 80% sequence similarity to the polypeptide of SEQ ID NO: 1, is increased by any means, and wherein said bacterial strain secretes SAM into the culture medium. The enablement provided is not commensurate in scope with the claims due to the extremely large number of SAM synthetases required by the claimed method for which there is no structure disclosed, as well as the unknown methods which would result in (1) secretion of SAM from any bacterial strain, and (2) a bacterial strain to have increased SAM synthetase activity. In the instant case, the specification enables a method for the production of SAM, wherein said method comprises the steps of (1) culturing an *E. coli* strain modified such that the enzymatic activity of the *E. coli* SAM synthetase of SEQ ID NO: 1 is increased by transforming said *E. coli* strain with an inducible plasmid that comprises a nucleic acid encoding the polypeptide of SEQ ID NO: 1, and (2) recovering said SAM.

The amount of direction or guidance presented and the existence of working examples. The specification discloses a mutant *E. coli* cell which has been transformed with an inducible plasmid containing a DNA molecule encoding the polypeptide of SEQ ID NO: 1 and 11, and the production of SAM by culturing said transformed *E. coli* cell, as working examples. However, the specification fails to disclose (1) how to secrete SAM from *E. coli* or any bacterial strain, (2) the structures of other SAM synthetases, (3) structural elements required in the variants of the polypeptide of SEQ ID NO: 1 recited such that those variants would also display SAM synthetase activity, or (4) how to increase the activity of

a SAM synthetase in a bacterial strain besides transforming said bacterial strain with an inducible plasmid containing a DNA molecule encoding a SAM synthetase, such as enhancers of SAM synthetase activity, mutations which would result in increased enzymatic activity, or transcription enhancers of any gene encoding a SAM synthetase. It should be noted that while the specification discloses the presence of SAM in the culture medium at 24 and 48 hours after induction, the specification does not provide any evidence which would suggest that the presence of SAM in the culture medium is the result of transport from the cytoplasm to the culture medium, which is how one of skill in the art would interpret the term "secretion", such as further transformation of the *E. coli* cell disclosed with genes encoding SAM transport proteins, or any suggestion as to the presence of some cell mechanism which would transport SAM to the extracellular medium. Thus, it appears that the presence of SAM in the culture after 24/48 hours is due to cell lysis.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any SAM synthetase or the structure of any variant of the polypeptide of SEQ ID NO: 1 having SAM synthetase activity. Furthermore, the neither the specification nor the art provide any teaching or guidance as to how the structures of those SAM synthetases known in the art correlate with that enzymatic activity such that one of skill in the art would know which structural modifications are required to obtain enhanced SAM synthetase activity. The art clearly teaches that structural changes in a protein to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland

Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes. With regard to SAM secretion to the extracellular medium, it is reiterated herein that the specification teaches that there is no SAM transport system in *E. coli* (page 4, last paragraph) and post-filing art by Tucker et al. (J. Bacteriol. 185(10):3031-3035, May 2003) discloses the first bacterial (*R. prowazekii*) AdoMet (SAM) transporter (page 3031, right column, first complete paragraph). Thus, in view of the absence of a transport system for SAM in *E. coli* or other bacterial strains, and in view of the teachings of the specification and the art, one of skill in the art would have to conclude that SAM secretion in a bacterial cell is unpredictable.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a protein were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all proteins having SAM synthetase activity. In addition, it was not routine in the art to screen by trial and error for (1) essentially an infinite number of mutations in either the regulatory region of a gene or in the coding region of a gene to determine which ones result in increased SAM synthetase activity, as recited in the claims, (2) all possible enhancers of SAM synthetase activity such as chemicals and the products of other genes, (3) all possible transcription enhancers of genes encoding SAM synthetases such as chemicals and the products of other genes, or (4) all SAM transport proteins which would be active in any bacterial strain. In the absence of some knowledge or guidance as to (1) a

correlation between structure and the required enzymatic activity, (2) the structural variability of SAM synthetases and the extent of such variability, (3) the structural changes required in any SAM synthetase which would result in an increase of enzymatic activity, (4) the structural changes required in the regulatory elements of any gene encoding a SAM synthetase such that the synthesis of the gene products can be increased, (5) the structure of enhancers of the required enzymatic activity, (6) the structure of molecules capable of enhancing transcription of genes encoding SAM synthetases, and (7) mechanisms which would allow secretion of SAM to the medium and/or transport proteins which would allow transfer of SAM from the cytoplasm to the medium, one of skill in the art would have to test an essentially infinite number of proteins/compounds to determine which ones have SAM synthetase activity, enhance SAM synthetase activity, enhance transcription of SAM synthetase genes, and transport SAM to the extracellular medium.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, as well as secretion of SAM, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Art of Interest

18. As indicated in the specification (page 5, first complete paragraph), Alvarez et al. (Biochem. J. 301:557-561, 1994; EP 0647712 published 4/12/1995; cited in the IDS and the specification) teach a method to produce SAM by transforming *E. coli* with an inducible plasmid comprising cDNA encoding a rat liver SAM synthetase. Alvarez et al. teach that SAM accumulates intracellularly when the

transformed *E. coli* cells are induced with IPTG (Biochem. J. 301:557-561, page 559, left column, last paragraph, Determination of intracellular AdoMet concentration; EP 0647712 page 4, lines 20-32). Also, as indicated in the specification (page 4, last paragraph), Markham et al. (J. Biol. Chem. 255(19):9082-9092, 1980) teach an *E. coli* containing a *metK* plasmid (metK encodes SAM synthetase) which produces 80X more SAM synthetase than wild-type *E. coli* (page 9086, right column, first paragraph under Discussion). The *E. coli* cell of Markham et al. produces *E. coli* SAM synthetase.

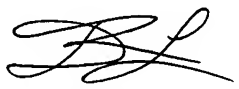
Conclusion

19. No claim is in condition for allowance.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
September 7, 2006